REMARKS

Claims 1, 2, 5, 6, 9, 10, 12, 13, 30, 33, 34, 36, 37, 44-52, 54-60, and 62-74 were pending. Claim 1, 6, 9, 13, 34, 37, 46, 55, 56, 62, 64, 67-70, 73, and 74 have been amended herein and new claims 75-77 have been added herein. Claims 3, 4, 7, 8, 11, 14-29, 31, 32, 35, 38-43, 53 and 61 were previously canceled. Accordingly, claims 1, 2, 5, 6, 9, 10, 12, 13, 30, 33, 34, 36, 37, 44-52, 54-60, and 62-77 are pending and under examination.

Support for amended claims 1, 6, 9, 13, 34, 37, 46, 55, 56, 62, 64, 67-70, 73, and 74 and new claims 75-77 may be found in the claims and specification as originally filed. Accordingly, these changes do not involve new matter and Applicants respectfully request entry of these changes.

Support for amended claim 1 may be found in the specification as originally filed at page 26, lines 9-15; page 27, lines 15-28; and page 47, Example 1.

Support for amended claim 6 may be found in the specification as originally filed at page 19, lines 21-31 and page 20, lines 1-5.

Support for amended claim 9 may be found in the specification as originally filed at page 7, lines 10-18; page 25, lines 29-31; page 26, lines 1-7; and page 27, lines 15-28.

Support for amended claim 13 may be found in the specification as originally filed at page 19, lines 21-31 and page 20, lines 1-5.

Support for amended claim 34 may be found in the specification as originally filed at page 27, lines 15-28 and page 47, Example 1.

Support for amended claim 37 may be found in the specification as originally filed at page 19, lines 21-31 and page 20, lines 1-5.

Support for amended claim 46 may be found in the specification as originally filed at page 19, lines 21-31 and page 20, lines 1-5.

Support for amended claim 55 may be found in the specification as originally filed at page 27, lines 15-28 and page 31, lines 9-16.

Support for amended claim 56 may be found in the specification as originally filed at page 27, lines 15-28; page 31, lines 9-16; and Figure 15.

Support for amended claim 62 may be found in the specification as originally filed at page 7, lines 10-18.

The amendment to Claim 64 merely corrects a grammatical error and corrects the plural term "chemotherapeutic agents" to the singular term "chemotherapeutic agent" to conform the term to the singular verb "is".

Support for amended claim 67 may be found in the specification as originally filed at page 19, lines 21-31; page 22, lines 3-15; page 27, lines 15-28; and page 41, lines 26-28.

Support for amended claim 68 may be found in the specification as originally filed at page 19, lines 21-31; page 27, lines 15-28; and page 41, lines 17-19.

Support for amended claim 69 may be found in the specification as originally filed at page 19, line 31; page 20, lines 1-2; page 27, lines 15-28; and page 41, lines 17-19.

Support for amended claim 70 may be found in the specification as originally filed at page 19, line 31; page 20, lines 1-2; page 27, lines 15-28; page 34, lines 16-19; and page 72, lines 17-19.

Support for amended claim 73 may be found in the specification as originally filed at page 27, lines 15-28; page 35, lines 8-9; page 38, lines 7-9; and page 41, lines 17-19.

Support for amended claim 74 may be found in the specification as originally filed at page 27, lines 15-28; page 34, lines 16-19; page 35, lines 8-9; page 38, lines 7-9; and page 72, lines 17-19.

Support for new claim 75 may be found in the specification as originally filed at page 28, lines 13-18.

Support for new claim 76 may be found in the specification as originally filed at page 27, lines 9-13 and lines 30-31 and page 28, lines 1-5.

Support for new claim 77 may be found in the specification as originally filed at page 47, Example 1.

Entry of the amendments and the foregoing remarks in the file of the above-captioned patent application is respectfully requested.

In accordance with the changes to the claims and the remarks that follow, Applicants respectfully request reconsideration of the outstanding rejections.

ITEM 1: APPEAL BRIEF

The Office acknowledges receipt of the Appeal Brief filed on December 26, 2007, and received by the Office on December 28, 2007, and reopens prosecution of the application with new grounds of rejection in the Office Action of April 21, 2008.

The Office indicates that Applicants must file a response to the April 21, 2008, Office Action ("the April 21 Office Action") under 37 C.F.R. §1.111 or file a Notice of Appeal under 37 C.F.R. §41.31.

ITEM 2: STATUS OF CLAIMS

The Office acknowledges that Claims 1, 2, 5, 6, 9, 10, 12, 13, 30, 33, 34, 36, 37, 44-52, 54-60, and 62-74 of this application are pending and that Claims 3, 4, 7, 8, 11, 14-29, 31, 32, 35, 38-43, 53 and 61 were previously canceled.

No response is due for this item.

ITEM 3: SPECIES ELECTION

The Office acknowledges the Applicants' election of the following species with traversal:

the alkylating agent is busulfan;
the first ligand is soluble CTLA4;
the second ligand is anti-CD40 antibody, and
the targeted condition is solid organ or tissue/cellular transplant.

The Office has indicated that in the interest of compact prosecution, and in view of enablement issues under 35 U.S.C. §112, first paragraph, the Office has extended the

search to include another alkylating agent, cyclophosphamide, in addition to busulfan. Therefore, claims 1-6, 9-13, 17, 28-37, 44-52, 54-60 and 62-74, are being examined in the instant application, to the extent that they read on the elected species.

No response is due for this item.

ITEM 4

The Office did not indicate which statute of Title 35 USC is being cited in the outstanding Office Action with respect to this Item. The Office also indicated that this Action is in response to Applicants' arguments filed in Applicants' Appeal Brief dated December 26, 2007 and the rejections of record can be found in the previous Office Action.

Further, the Office indicates that new grounds of rejection have been set forth in the April 21 Office Action. Specifically the Office indicates that it is providing prior art references showing administration of an alkylating agent after the T cell depleted bone marrow (TDBM) is administered to a subject.

No response is due for this item. Rebuttal arguments against the cited art will be presented below.

ITEM 5: PRIORITY

The Office takes the position that the filing date of the instant claims is deemed to be the filing date of priority application, U.S. Serial No. 60/303,142, filed July 5, 2001, rather than priority application U.S. Serial No. 60/264,528, filed January 26, 2001, hereinafter "the '528 application".

At page 4 of the Office Action, the Office alleges that the '528 application does not provide sufficient written description for

(a) "administering TDBM before, during and/or after a solid organ or tissue/cellular transplant";

(b) "subsequently administering an alkylating agent...(including busulfan)"; or

(c) "administering an (sic) costimulatory blockade before, during and/or after a solid organ or tissue/cellular transplant blockade (sic) which costimulatory blockade comprises a combination of a first ligand that interferes with binding of CD28 to either CD80 or CD86, and a second ligand that interferes with binding of CD154 to CD40", as currently claimed.

Further, the Office alleges that the '528 application, does not appear to provide sufficient written support for

- "all of the claimed dosage amounts and administration timing (e.g., see claims 30, 57-60, 62-63)"
- "all of the claimed characteristics of the claimed soluble CTLA4 molecule (e.g., see claims 44-50, 65-, 73-74)"
- "all of the claimed alkylating (sic) agents (e.g., see claims 63-64)" nor
- "all of the claimed ligands for CD40 (e.g., see claims 52 and 54-55)"

currently recited in the instant application.

Applicants respectfully disagree that the '528 application, does not sufficiently describe the specific specification passages *supra*.

Contrary to the Office's position that the '528 application discloses a "single dose of busulfan prior to the transplantation (i.e. intravenous infusion) of T cell-depleted bone

marrow cells", data supporting passages (a)-(c) *supra* can be found in the '528 application as follows.

Applicants' support for passage (a) ("administering TDBM before, during and/or after a solid organ or tissue/cellular transplant") may be found in the skin graft experiments, at pages 4 and 5 of the '528 application. These experiments clearly describe administering TDBM on day 0, i.e. same day or "during" the transplant, and on day 6, i.e. after the transplant (page 4, line 12). The skin graft (transplant) was done on day 0 (page 4, line 13). The data is shown in Figure 2A. Figure 2A clearly supports a claim of administering TDBM during and after a transplant. The claim of administering TDBM before the transplant is shown in the experiments described on pages 4-5 of the '528 application, in which the mice which were administered TDBM on days 0 and 6 (page 4, line 12) and were re-challenged with skin transplants 100 days after the original transplant/protocol (page 5, lines 5 and 6).

Applicants' support for passage (b) ("subsequently administering an alkylating agent") (e.g., busulfan) is in the experiment to induce hematopoietic chimerism (page 2, lines 18-23) and the skin graft experiment (page 4, lines 8-13); data from the experiments are shown in Figures 1A and 2, respectively, of the '528 application. In the experiments, Applicants describe using the alkylating agent busulfan on day 5 to induce hematopoietic chimerism and prolong skin graft survival. Thus, in one experiment, TDBM cells are administered on day 0, busulfan is administered on day 5, and TDBM cells are administered on day 6 and in the second experiment, TDBM cells and a skin graft are administered on day 0, busulfan is administered on day 5, and TDBM cells are administered on day 6.

Regarding Applicants' support for passage (c) ("administering an immunosuppressive composition before, during and/or after a solid organ or tissue/cellular transplant"), the

immunosuppressive composition (e.g., costimulatory blockade (CB) comprising a combination of a first ligand that interferes with binding of CD28 to either CD80 or CD86, and a second ligand that interferes with binding of CD154 to CD40), is used in the experiment to induce hematopoietic chimerism (page 2, lines 21-22) and the skin graft experiment described in the '528 application (page 4, lines 8-12). The data is shown in Figures 1A and 2. Since the co-stimulatory blockade is described at page 2, line 22, of the '528 application, as being administered on days 0, 2, 4, 6, 14, and 28, and the skin graft is administered on day 0, the use of the terms "before, during and/or after" is supported.

The Office alleges that the disclosure of the'528 application is limited to a species of alkylating agent (e.g., busulfan) and "does not provide sufficient direction and guidance to the written description of the currently claimed "limitations" "wherein the alkylating agent is selected from a group consisting of alkylsulfonates, nitrogen mustards, oxazaposporines, nitrosoureas" as well as all of the currently claimed dosage amounts and administration timing."

Applicants respectfully disagree.

The written description requirement for a claimed genus under paragraph 1 of 35 U.S.C. §112, may be satisfied through sufficient description of a representative number of species by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Regents of the Univ. of Calif. V. Eli Lily & Co., 119 F.3d at 1568, 43 USPQ2d at 1406 (Fed. Cir. 1997). In In re Herschler, 591 F.2d 693, 697, 200 USPQ 711, 714 (CCPA 1979), disclosure of corticosteroid in DMSO was found sufficient to support

claims drawn to a method of using a mixture of a "physiologically active steroid" and DMSO, because "use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description."

Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. The written description requirement of paragraph 1, 35 U.S.C. §112, does not require the disclosure of every species encompassed by the claims. In re Angstadt and Griffin, 537 F.2d 498, 190 USPQ 214, 218 (CCPA 1976)).

A person of ordinary skill in the art would be lead to the class of compounds described as alkylating agents, with Applicants' disclosure of busulfan and description of its functional properties.

With respect to the currently claimed "dosage amounts and administration timing," Applicants have provided ranges of dosages and timing of the administration of reagents such that a person of ordinary skill in the art, typically a physician, would understand appropriate dosages in view of Applicants' disclosures and the history of individual subjects (e.g. age, weight, health) (specification at page 27, lines 15-28).

The Office also maintains that the description in the'528 application does not provide support for "all of the claimed characteristics of the claimed soluble CTLA4 molecule (e.g., see claims 44-50, 65-, 73-74)," and "all of the claimed ligands for CD40 (e.g., see claims 52 and 54-55" (April 21 Office Action, page 4, 5th paragraph).

With respect to the "claimed characteristics of the soluble CTLA4 molecule," in claims 44-50, et seq., these claims recite the structural characteristics of the soluble CTLA4 molecule required to accomplish the function of the reagent recited in Claim 1, i.e. "blocking T cell costimulatory signals with a first ligand that interferes with binding of CD28 to either CD80 or CD86." Support for these structural characteristics is found throughout the specification, for example at page 19, lines 16-19; page 20, line 27 to page 21, line 21; page 35, lines 6-9 and Figures 15 and 20.

Further, the Office alleges that the '528 application does not appear to support the instant claims as it only provides for CTLA4Ig and the anti-CD40L monoclonal antibody, and that a generic or sub-generic disclosure cannot support a species unless the species is specifically described. Again the Office seeks to limit the claims to species, CTLA4Ig and anti-CD40L monoclonal antibody, unless all other species are described. This is simply not the law as set forth above. In re Angstadt and Griffin, 537 F.2d 498, 190 USPQ 214, 218 (CCPA 1976).

Applicants have provided sufficient written description in the '528 application, of the functional and structural characteristics of the first and second ligands for the costimulatory blockade, such that a person of skill in the art could select additional species having the described functional and structural characteristics, i.e. interfering with binding of CD28 to either CD80 or CD86, and interfering with binding of CD154 to CD40.

Accordingly, the disclosure of the '528 application supports the instant claims and Applicants are entitled to the January 26, 2001, filing date. Applicants request that the Office withdraw the rejection.

ITEM 6: ATCC DEPOSIT

The Office acknowledges Applicants' deposit of biological materials with ATCC deposited as ATCC Numbers 68629 and 10762 in the Appeal Brief filed December 26, 2007 (and received by the Office on December 28, 2007) and withdraws the rejection of claims 67-70 under 35 U.S.C. §112, first paragraph, enablement.

No response is due.

ITEM 7: REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH – ENABLEMENT

At page 6 of the outstanding Office Action, the Office reiterated its rejection of claims 47-48 and currently rejects claims 49-50 and 73-74 under 35 U.S.C. §112, first paragraph, alleging that while the specification is enabling for the specific mutant CTLA4 molecules, such as the L104EA29YIg molecule disclosed in the specification as filed, it does not reasonably provide enablement for "any CTLA4 mutant molecule," to be employed as an immunosuppressive agent in the instant claimed methods.

Applicants respectfully disagree for reasons of record and as discussed *infra.*

Applicants' Argument

"The essential question here is whether the scope of enablement ... is as broad as the scope of the claim[s]." Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1212 (Fed. Cir. 1991). It would not have required undue experimentation to practice of the full scope of the claimed invention. Other than the fact that molecular biology is an unpredictable art, the remaining Wands factors favor Appellants, particularly "the amount of direction or guidance presented", "the state of the prior art" and "the relative skill of

those in the art," In re Wands, 858 F.2d 731, 736 (Fed. Cir. 1988). Even the factor of "the predictability or unpredictability of the art" weighs in favor of Appellants, as evidenced by the prior art teachings and Appellants' Specification. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. In re Angstadt, 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976). What is required it that there be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill in the art how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. In re Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991); In re Abad, 2008 WL 904456 (BPAI 2008). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." Atlas Powder Co., v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576 (Fed. Cir. 1984).

In the instant application, there is significant disclosure of methods for obtaining mutant CTLA4 molecules. Specifically, Applicants provide methods for screening CTLA4 mutants for their binding capacity (Example 9, pages 71-83, of the instant application). Further, Applicants provide examples of over thirty mutant molecules (Tables I and II at pages 82 and 83 and on page 70, lines 22-25), including their entire nucleotide sequences, and described the required functions for other members of the class of proteins (page 75, line 28 through page 78, line 24 and page 79, line 20 through page 81).

In addition, Applicants provide herewith evidence of post-filing confirmatory data of numerous additional mutants within the scope of Claim 38 in the present application, in the form of U.S. Patent No. 7,105,166, Linsley et al., "Soluble CTLA4 Mutant Molecules and Uses Thereof," issued September 12, 2006 (hereafter '166 patent)(Exhibit A). Specifically,

in Table II of the '166 patent, Applicants show examples of twenty-four (24) single-site CTLA4Ig mutants with their CD86 binding activity. Further, Table III of the '166 patent shows examples of ten (10) double-site CTLA4Ig mutants with their CD86 binding activity. Finally, Table IV of the '166 patent shows examples of six (6) triple-site CTLA4Ig mutants with their CD86 binding activity.

Regarding claims 49-50 and 73-74, Applicants point out that they are directed to specific CTLA4 molecules with sequences specified by SEQ ID NO:4 or SEQ ID NO:13 rather than to "any CTLA4 mutant molecule" as the Office alleges. Accordingly, these claims are enabled.

Regarding claims 47-48 directed to soluble CTLA4 mutant molecules, Applicants traverse the rejection because Applicants provide methods for screening CTLA4 mutants for their binding capacity (Example 9, pages 71-83, of the instant application). The binding kinetics of several CTLA4 mutant molecules to CD80 and CD86 are shown in Table I. Further, Applicants provide examples of over thirty mutant molecules (Tables I and II at pages 82 and 83 and on page 70, lines 22-25), including their entire nucleotide sequences, and described the required functions for other members of the class of proteins (page 75, line 28 through page 78, line 24 and page 79, line 20 through page 81).

Practice of the claimed invention does not require undue experimentation.

35 U.S.C. § 112, first paragraph, requires Applicants to teach how to make and use the invention, without undue experimentation. The law is clear. Applicants are not required to disclose every species encompassed by the claims (In re Angstadt and Griffin, 537 F.2d 498, 190 USPQ 215, 218 (CCPA 1976)). Moreover, despite the fact that Applicants do not disclose every known CTLA4 mutant molecule, the identification of other species in the class would not entail undue experimentation, because Applicants' disclosure outlines

a number of different assays for the identification of CTLA4 mutant molecules.

Accordingly, the specification enables over thirty CTLA4 mutant molecules; enables those skilled in the art to identify additional CTLA4 mutants to be used in the claimed methods of the invention; and enables the binding of CTLA4 mutant molecules to CD80 and/or CD86.

In view of the preceding remarks, Applicants respectfully request that the Office reconsider and withdraw the rejection set forth in the Office Action.

ITEM 8: REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH, WRITTEN DESCRIPTION – NEW GROUNDS FOR REJECTION

At page 8 of the outstanding Office Action, the Office newly rejects claims 47-50 and 73-74 under 35 U.S.C. §112, first paragraph, written description, alleging that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Office alleges that the "claims recite and encompass 'a soluble CTLA4 mutant molecule that interferes with the binding of CD28 to CD80 and/or CD86' in the absence of a (sic) those structures or elements of CTLA4 mutant that are important or critical" to such molecules. In other words, the Office alleges that "the instant specification fails to provide a disclosure of which residues are required for the 'soluble CTLA4 mutant molecule' 'to interfere with the binding of CD28 to CD80 and/or CD86'." (page 11).

Additionally, the Office seems to be alleging that a representative number of species has not been reduced to practice in the subject application. The Office states at page 10, 4th paragraph that, "if a claimed genus does not show actual reduction to practice for a

representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics" (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday, January 2001).

Applicants respectfully disagree.

The references cited by the Office (i.e. Ngo et al., Attwood, Skolnick et al., Coyle et al., and Metzler et al.) and the caselaw cited by the Office (i.e. Enzo, Vas-Cath, University of Rochester) were previously discussed in the responses to the Office Actions dated February 28, 2005, November 29, 2005, June 14, 2006, and March 29, 2007, in relationship to the 35 U.S.C. §112, first paragraph, enablement rejections. Applicants' traversal is of record.

"The written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics.'" Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 964 (Fed. Cir. 2002).

The instant facts comply with many of the factors cited by Enzo as demonstrating compliance with the written description requirement. The amino acid sequence of CTLA4 mutant molecules is disclosed in the specification at page 18, lines 13-31; page 19, lines 1-19; page 20, lines 7-17 and Figure 19. Moreover, the specification directly couples structure with function in demonstrating that the mutations have the required function (page 24, lines 5-22). Here, as Applicants have pointed out, the specification provides significant guidance regarding which structural features in the CTLA4 mutant

molecules are responsible for the function of interfering with the binding of CD28 to CD80.

The instant facts are distinguishable from those in Ex Parte Kubin, 83 USPQ2d 1410, 1416, 1417 (BPAI 2007). In Kubin, the applicants disclosed nucleic acids encoding the NAIL protein at issue and fusion proteins comprising NAIL, but did not disclose any variants in the region where 80% identity was required. Id. at 1415. "The Specification [did] not disclose a correlation between function (binding to CD48) and structure responsible for binding to CD48 (other than the entire extracellular domain)." Id. at 1416. In the present case, CTLA4 proteins are now a well characterized family of proteins. For example, U.S. Patent No. 7,105,166 provides over thirty mutant CTLA4 proteins (see Tables II - IV).

It is "not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention." Capon v. Eshhar, 418 F.3d 1349, 1359 (Fed. Cir. 2005).

In the instant case, there is significant information to characterize the generic invention, ranging from the capacity to generate, identify and screen members of the genus, and large numbers of different mutations which characterize structure/function relationships. Thus, the Specification does describe the recited CTLA4 mutant molecules sufficiently to allow a person skilled in the art to determine whether a given protein is within the scope of the instant claims. In re Abad, 2008 WL 904456 (BPAI 2008).

Regarding claims 49-50 and 73-74, Applicants point out that they are directed to specific CTLA4 molecules with sequences specified by SEQ ID NO:4 or SEQ ID NO:13 rather

than to "any CTLA4 mutant molecule as the Office alleges." Accordingly, the specification provides written description for these claims.

Regarding claims 47-48 Applicants traverse the rejection because Applicants provide methods for screening CTLA4 mutants for their binding capacity (Example 9, pages 71-83, of the instant application). The binding kinetics of several CTLA4 mutant molecules to CD80 and CD86 are shown in Table I. Further, Applicants provide examples of over thirty mutant molecules (Tables I and II at pages 82 and 83 and on page 70, lines 22-25), including their entire nucleotide sequences, and described the required functions for other members of the class of proteins (page 75, line 28 through page 78, line 24 and page 79, line 20 through page 81).

Regarding the Office's allegation that a representative number of species has not been reduced to practice, Applicants point out that providing a sequence for a biological molecule is actual reduction to practice (see Fiers v. Revel, 984 F.2d 1164, 25 USPQ2d 1601 (Fed. Cir. 1993) and Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)). Accordingly, Applicants have reduced to practice over thirty CTLA4 mutant molecules.

Accordingly, the specification provides a clear written description of over thirty CTLA4 mutant molecules; provides written description to guide those skilled in the art to identify additional CTLA4 mutants to be used in the claimed methods of the invention; and provides written description of the binding of multiple CTLA4 mutant molecules to CD80 and/or CD86.

In view of the preceding remarks, Applicants respectfully request that the Office reconsider and withdraw the rejection set forth in the Office Action.

ITEMS 9-11: REJECTIONS UNDER 35 U.S.C. §103(a) – NEW GROUNDS OF REJECTION

The Legal Standard for 35 U.S.C. §103

Obviousness is a question of law based on findings of underlying facts relating to the prior art, the skill of the artisan, and objective considerations. See Graham v. John Deere Co., 383 U.S. 1, 17, 86 S.Ct. 684, 694, 148 USPQ 459, 467 (1966). To establish a *prima facie* case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant. In re Raynes, 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). Obviousness can not be established by hindsight combination to produce the claimed invention. In re Gorman, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991).

When the references are in the same field as that of the applicant's invention, knowledge thereof is presumed. However, the test of whether it would have been obvious to select specific teachings and combine them, as did the applicant, must still be met by identification of some suggestion, teaching, or motivation in the prior art, arising from what the prior art would have taught a person of ordinary skill in the field of the invention. In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988). As discussed in Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985), it is the prior art itself, and not the applicant's achievement, that must establish the obviousness of the combination.

As stated in MPEP §2143, the Office must articulate Exemplary rationales that may support a conclusion of obviousness. For example, in MPEP §2143(g), an exemplary

rationale in support of obviousness is:

> "Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

The teaching or suggestion to make the claimed combination, and the reasonable expectation of success, must both be found in the prior art, not in the Applicant's disclosure (In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)).

The Supreme Court recently addressed the issue of obviousness in KSR International Co. v. Teleflex Inc., --- U.S. ----, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007) (hereinafter "KSR"). The Court stated that the Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966), factors still control an obviousness inquiry. Those factors are: 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness. KSR, 127 S.Ct. at 1734 (quoting Graham, 383 U.S. at 17-18, 86 S.Ct. 684). The Supreme Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. KSR, 127 S.Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM ("teaching, suggestion, motivation") test and the Graham analysis." Id. As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. Id.

For a finding of obviousness, there must be predictability or reasonable expectation of success in achieving the claimed invention when prior art is combined. In re O'Farrell, 853 F.2d 894, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

The Office Has Not Established A Prima Facie Case Of Obviousness

The Office has not established a prima facie case of obviousness because none of the necessary criteria for obviousness under 35 U.S.C. §103 have been met.

Applicants' Invention

The present invention as shown in independent claims 1, 9, 34, 55 and 56, provides methods for inhibiting or reducing rejection of a solid organ or tissue/cellular transplant in a subject comprising the following sequence of steps: administering T cell depleted bone marrow cells to the subject before, during or after the solid organ or tissue/cellular transplant; thereafter administering an alkylating agent (e.g., busulfan) to the subject in an amount that facilitates mixed chimerism; and administering a subsequent dose of T cell depleted bone marrow. Additionally, an immunosuppressive composition that blocks T cell costimulatory signals can be administered in the subject before, during or after the transplant.

Also, the present invention, as shown in independent claims 62 and 63, provides methods for inhibiting or reducing rejection of solid organ or tissue/cellular transplant in a subject comprising administering: two doses of T cell depleted bone marrow, an immunosuppressive composition that blocks T cell costimulatory signals, and an alkylating agent at specific dosages.

ITEM 9: REJECTION UNDER 35 U.S.C. §103(a)

The Office rejects Claims 1-6, 9-13, 17, 30, 33-37, 44-52, 54-63 and 64 under 35 U.S.C. §103(a), as allegedly unpatentable over Sykes et al. (U.S. Patent No. 6,514,513), in view

of art known practice and modes of administration of alkylating agents such as busulfan/cyclophosphamide at various times to meet the needs of the patients, as acknowledged on pages 26-27 of the instant specification and as evidenced by Andersson et al. (U.S Patent Nos. 5,430,057 and 5,559,148) (1449, Exhibits 2 and 4), Slattery et al. (Therapeutic Drug Monitoring 20:543-549, 1998) and Hassan et al. (Blood 84:2144-2150, 1994), The Merck Manual of Diagnosis and Therapy, 17th Ed. (edited by Beers et al.), Shichi et al., (U.S. Patent No. 4,843,092), Strom et al. (Therapeutic Immunology edited by Austen et al.), Sykes et al. (Nature Medicine 3:783-787, 1997) and Wekerle et al. (J Exp Med, 187:2037-2044, 1998) for reasons of record and in further view of Reinherz et al. (U.S. Patent 4,443,427), Tomita et al. (J. Immunol. 164:34-41, 2000) (1449, Exhibit #274), Bingaman et al. (Transplantation 69:2491-2496, 2000) (1449, Exhibit #193), Larsen et al. (Curr. Opin. Immunol. 9:641-647) (1449, Exhibit #188), and Schaub et al. (J. Allergy and Clin. Immunol. 99:5206, abstract 843, 1997) (1449, Exhibit #264).

Applicants respectfully disagree.

Sykes, U.S. Patent No. 6,514,513 (Sykes '513)

Sykes discloses a method of promoting graft acceptance (e.g., skin graft), by a recipient mammal, wherein the graft is from a donor mammal of a second species. The method includes: administering to the recipient, an inhibitor of immune reactions, (e.g., either CTLA4Ig or anti-CD40 ligand monoclonal antibodies); administering low dose whole body irradiation; introducing hematopoietic stem cells (e.g., a bone marrow preparation) into the recipient mammal; and then preferably, implanting the graft in the recipient. Sykes proposes that the hematopoietic cells prepare the recipient for the graft that follows, by inducing tolerance at both the B-cell and T-cell levels (Sykes '513 at column 1, lines 49-52).

Sykes uses irradiation in the methods described (Sykes '513 at column 22, lines 36-40; column 23, lines 15-19; column 24, lines 34-36; column 25, lines 9-12; and column 27, lines 52-55) but also suggests that busulfan may be used in lieu of irradiation, to create hematopoietic space. However, this suggestion is not supported by any description of or guidance for substitution of busulfan for irradiation. There is no reasonable expectation of success if busulfan is substituted for whole body irradiation. There is no data supporting a direct correlation between the irradiation dosage and the necessary busulfan dosage to be administered, to facilitate mixed hematopoietic chimerism. In fact, because the art (Hassan et al., discussed *infra*), teaches that total body irradiation is superior to busulfan in terms of patient survival, a person of skill in the art would be led away from substituting busulfan for irradiation.

Specifically, Sykes fails to teach the use of busulfan together with other agents, in a specific sequence as presently claimed to facilitate mixed hematopoietic chimerism, or the effective dosage of busulfan for such use. Additionally, Sykes fails to teach the therapeutic sequence of the claimed invention as disclosed in independent claims 1, 9, 34, 55, 56, 62 and 63. The claimed methods require: T cell depleted bone marrow administered to a subject; an alkylating agent administered to a subject after the bone marrow; additional T cell depleted bone marrow administered to a subject after the alkylating agent; and then administration of a costimulatory blockade to a subject. Further, Sykes fails to teach the specified dosages of busulfan recited in claims 62 and 63.

The combination of Sykes '513 and the additional references (discussed *infra*) cited by the Office does not rectify the deficiencies in Sykes and does not render the claimed invention obvious.

Andersson et al., U.S Patent Nos. 5,430,057 (the '057 patent) and 5,559,148 (the '148 patent)

The '057 and '148 patents have identical specifications since the '148 patent is a continuation of the '057 patent. Accordingly, the specifications and claims of the '057 and the '148 patents are discussed together herein. The '057 and the '148 patents provide methods for use of parenteral formulations of busulfan, in the clinical treatment of human neoplasms, with therapy based on parenteral preparation alone, or in combination with other cytotoxic agent(s). Additionally, these patents provide formulations to increase solubility of busulfan, design of a chemically stable formulation of busulfan that is suitable for parenteral administration, and techniques to extract busulfan from blood, as well as pharmacokinetics of commercially available busulfan, and busulfan when solubilized in polyethylene glycol.

The '057 and the '148 patents fail to teach what the primary reference fails to teach, namely, the use of alkylating agents, e.g., busulfan, together with other agents of the claimed methods for facilitating mixed hematopoietic chimerism, the administration of agents in a specific sequence and the effective dosage of busulfan for such use. Moreover, these patents fail to teach or suggest the use of busulfan for inhibition or reduction of rejection of solid organ transplants.

Nothing in the disclosure of these patents provides "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" to support a finding of obviousness. KSR, 127 S.Ct. at 1731.

Accordingly, the combination of the Sykes '513 and the '057 and '148 patents does not render obvious the claimed methods.

Slattery et al., Therapeutic Drug Monitoring, 1998, 20:543-549

Slattery et al. provide methods for use of busulfan, to ablate marrow before hematopoietic stem cell transplantation, and the use of high levels of busulfan, in combination with cyclophosphamide, to treat patients with chronic myeloid leukemia. Further, Slattery et al. state that the therapeutic window for busulfan is narrow, and disease and graft-source dependent.

Slattery et al. fail to teach what the primary reference fails to teach, namely, the use of busulfan together with other agents of the claimed methods, for facilitating mixed hematopoietic chimerism, the administration of agents in a specific sequence, and the effective dosage of busulfan for such use. Further, Slattery et al. do not teach or suggest the use of busulfan for inhibition or reduction of rejection of solid organ transplants.

Nothing in this disclosure provides "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" to support a finding of obviousness. KSR, 127 S.Ct. at 1731.

Accordingly, the combination of the Sykes '513 and the Slattery et al. reference does not render obvious the claimed methods.

Hassan et al., Blood, 1994, 84:2144-2150

Hassan et al. provides methods for use of busulfan in patients only undergoing bone marrow transplantation and evaluates the bioavailability of busulfan. Additionally, Hassan et al. note that although busulfan has been introduced as an alternative to total body irradiation (TBI), TBI treatment of patients conferred a survival advantage over

busulfan treated patients (page 2144, column 1, paragraph 2).

Hassan et al. fail to teach what the primary reference fails to teach, namely, the use of busulfan together with other agents of the claimed methods, for facilitating mixed hematopoietic chimerism, the administration of agents in a specific sequence, and the effective dosage of busulfan for such use. Further, Hassan et al. do not teach or suggest the use of busulfan for inhibition or reduction of rejection of solid organ transplants.

Hassan et al. teach that busulfan has a higher mortality rate compared to TBI. Accordingly, Hassan et al. teach away from the use of an alkylating agent in the claimed methods.

In view of this teaching of Hassan et al., the combination of Hassan et al. with Sykes '513 is unwarranted, and fails to render the claimed methods obvious.

The Merck Manual of Diagnosis and Therapy, 17th Ed., edited by Beers et al., 1999

The Merck Manual (pages 1067-1074) teaches an overview of biology related to transplantation including the immunobiology of rejection, components of tissue compatibility and immunosuppression. Immunosuppressive drugs mentioned in the Merck Manual include corticosteroids, azathioprine, cyclophosphamide, cyclosporine and tacrolimus. Other immunosuppressive factors mentioned in the Merck Manual include monoclonal antibodies and irradiation.

The Merck Manual fails to teach what the primary reference (Sykes '513) fails to teach, namely, the use of alkylating agents, e.g., busulfan, together with other agents of the claimed methods, for facilitating mixed hematopoietic chimerism, the administration of agents in a specific sequence, and the effective dosage of busulfan for such use. Further,

the Merck Manual does not teach or suggest the use of busulfan for inhibition or reduction of rejection of solid organ transplants.

Moreover, nothing in this disclosure provides "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" to support a finding of obviousness. KSR, 127 S.Ct. at 1731.

Accordingly, the combination of the Sykes '513 and the Merck Manual reference does not render obvious the claimed methods.

Shichi et al., U.S. Patent No. 4,843,092

Shichi et al. teach an immunosuppressive agent comprising macrolide antibiotic(s) for suppressing rejection after organ transplantation and as an agent for treating immune diseases. The background section of Shichi et al. mentions that "[a]s immunosuppressive agents, there are known alkylating agents such cyclophosphamide" which can be used as agents for suppressing rejection which may occur after transplantation. Shichi et al. does not teach how to use any alkylating agent such as cyclophosphamide or busulfan (i.e., does not teach any methods of administration nor any dosages by itself or in combination with other agents).

Shichi et al. fail to teach what the primary reference (Sykes '513) fails to teach, namely, the use of an alkylating agent, e.g., busulfan, together with other agents of the claimed methods, for facilitating mixed hematopoietic chimerism, the administration of agents in a specific sequence, and the effective dosage of an alkylating agent, e.g., busulfan, for such use. Further, Shichi et al. do not teach or suggest the use of an alkylating agent, e.g., busulfan, for inhibition or reduction of rejection of solid organ transplants.

Moreover, nothing in this disclosure provides "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" to support a finding of obviousness. KSR, 127 S.Ct. at 1731.

Accordingly, the combination of the Sykes '513 and the Shichi et al. references does not render obvious the claimed methods.

Strom et al., Therapeutic Immunology edited by Austen et al., 1996

Strom et al. teach the use of multiple agents simultaneously, with each agent directed at a different molecular target, for immunosuppressive therapy. The agents cited by Strom et al. to be used in combination are: cyclosporine, tacrolimus (FK506), corticosteroids, azathioprine, mycophenolate mofetil, OKT3 monoclonal antibody, anti-IL-2 antibody, anti-IL-2 receptor antibody, anti-adhesion molecule antibody and rapamycin.

Strom et al. fail to teach what the primary reference fails to teach, namely, the use of an alkylating agent, e.g., busulfan, together with other agents of the claimed methods for facilitating mixed hematopoietic chimerism and tolerance induction, the administration of agents in a specific sequence, and the effective dosage of an alkylating agent, e.g., busulfan, for such use. Moreover, Strom et al. fail to teach or suggest the use of an alkylating agent, e.g., busulfan, for inhibition or reduction of rejection of solid organ transplants.

Moreover, nothing in this disclosure provides "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" to support a finding of obviousness. KSR, 127 S.Ct. at

1731.

Accordingly, the combination of the Sykes '513 and the Strom et al. reference does not render obvious the claimed methods.

Sykes et al., Nature Medicine 3:783-787, 1997

Sykes et al. teach donor specific T-cell tolerance induced by administering to a murine subject: 1) depleting anti-CD4 and anti-CD8 monoclonal antibodies to remove the host immune barriers to T cell allo-engraftment, 2) local thymic irradiation to produce space in the thymic compartment, and 3) a high dose of MHC-mismatched bone marrow cells.

Sykes et al. fail to teach what the primary reference (Sykes '513) fails to teach, namely, the use of an alkylating agent, e.g., busulfan, together with other agents of the claimed methods, for facilitating mixed hematopoietic chimerism, the administration of the agents in a specific sequence, and the effective dosage of an alkylating agent, e.g., busulfan, for such use. Sykes et al. do not teach or suggest the use of an alkylating agent, e.g., busulfan, for inhibition or reduction of rejection of solid organ transplants.

Moreover, nothing in this disclosure provides "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" to support a finding of obviousness. KSR, 127 S.Ct. at 1731.

Accordingly, the combination of the Sykes '513 and the Sykes et al. reference does not render obvious the claimed methods.

Wekerle et al., J Exp Med, 187:2037-2044, 1998

Wekerle et al. teach induction of transplantation tolerance by administering to a murine subject: 1) single injections of anti-CD40 ligand antibody and CTLA4Ig, 2) whole body irradiation, and 3) MHC-mismatched allogeneic bone marrow transplantation.

However, Wekerle et al. fail to teach what the primary reference (Sykes '513) fails to teach, namely, the use of an alkylating agent, e.g., busulfan, together with other agents of the claimed methods, for facilitating mixed hematopoietic chimerism, the administration of the agents in a specific sequence, and the effective dosage of an alkylating agent, e.g., busulfan, for such use. Moreover, Wekerle et al. fail to teach or suggest the use of an alkylating agent, e.g., busulfan, for inhibition or reduction of rejection of solid organ transplants.

Moreover, nothing in this disclosure provides "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" to support a finding of obviousness. KSR, 127 S.Ct. at 1731.

Accordingly, the combination of the Sykes '513 and the Wekerle et al. reference does not render obvious the claimed methods.

Reinherz et al., U.S. Patent 4,443,427

Reinherz et al. teach monoclonal antibodies specific to T cell surface antigen "T12" and use of anti-T12 in the treatment of medical disorders such as autoimmune diseases and graft versus host disease (GVHD) after transplantation of an organ/tissue. Busulfan (8 mg/kg), cytoxan (cyclophosphamide) (200 mg/kg) and anti-lymphocytic serum (0.2

mg/kg) were administered over eight days to a subject to condition the subject for transplantation of T cell depleted bone marrow (column 7, 3rd paragraph). However, the subject developed acute GVHD after the transplant and required multiple administration of anti-T12 to treat the GVHD (column 8, 1st paragraph).

Accordingly, Reinherz et al. fail to teach what the primary reference (Sykes '513) fails to teach, namely, the use of a combination of an alkylating agent e.g., busulfan or cyclophosphamide, together with other agents of the claimed methods, for facilitating mixed hematopoietic chimerism and for inhibition or reduction of rejection of solid organ transplants. Nor does Reinherz et al. teach the administration of the agents in a specific sequence or the effective dosage of busulfan for use in such a combination. Indeed, Reinherz et al. teach away from the claimed invention by showing that even the use of a combination of two alkylating agents (i.e. busulfan and cyclophosphamide) with an anti-lymphocytic serum could not induce graft tolerance.

In view of the teaching of Reinherz et al., the combination of the Sykes '513 patent with Reinherz et al. reference fails to render the claimed methods obvious.

Tomita et al., J. Immunol. 164:34-41, 2000

Tomita et al. experimented with several regimens to induce mixed chimerism and skin allograft tolerance (Tables I-III). The most successful regimen was administering four components to a subject: allogeneic spleen cells on day 0, two alkylating agents (i.e. 200 mg/kg cyclophosphamide and 25 or 50 mg/kg busulfan) on day 2 and T cell-depleted bone marrow from the same donor on day 3 (Table II). Unless the four component regimen was used, mixed chimerism and long-term skin graft acceptance were not induced (page 37, first column, 1st paragraph).

Contrary to the Office's allegation that Tomita et al. administered busulfan and cyclophosphamide the same day as spleen cells (Office Action page 13, second paragraph), Tomita et al.'s experimental conditions required the alkylating agents to be administered two days after the spleen cells (which were administered on day 0) and one day before the bone marrow in order to induce mixed chimerism and skin allograft tolerance. Additionally, the Office's reading of Tomita et al. at page 36, column 2 is incorrect (as set forth in the April 21 Office Action at page 13, 4th paragraph): busulfan was not administered on day 3, but on day 2; bone marrow was not administered at both days 2 and 3, only on day 3.

The Office asserts that administering the alkylating agents the "same" day as the spleen cells "provides for the obviousness of providing said alkylating agents subsequent to administering bone marrow, given the use of alkylating (sic) agents after administering hemopoietic cells had advantages when given at the same or nearly the same time." Applicants believe that the Office is alleging that spleen cells are hematopoietic cells and can be substituted for bone marrow administered to the subject prior to administering the alkylating agent as required in the claimed methods. Spleen cells are not bone marrow. Substituting spleen cells for bone marrow to achieve mixed hematopoietic chimerism is unsupported by any teaching, suggestion or motivation that such a substitution would result in a reasonable expectation of success to practice the claimed invention.

Tomita et al. also fail to teach the use of any costimulatory blockade molecules, much less using the combination of costimulatory blockade molecules together with an alkylating agent (e.g., busulfan or cyclophosphamide) and the bone marrow of the claimed methods, for facilitating mixed hematopoietic chimerism and inhibition or reduction of rejection of solid organ transplants. Nor do Tomita et al. teach the administration of the agents in the specific sequences claimed or the effective dosage of an alkylating agent for use in such a combination.

Moreover, nothing in this disclosure provides "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" to support a finding of obviousness. KSR, 127 S.Ct. at 1731.

Accordingly, the combination of the Sykes '513 and Tomita et al. reference does not render obvious the claimed methods.

Bingaman et al., Transplantation 69:2491-2496, 2000

Bingaman et al. teach a regimen to induce hematopoietic chimerism and graft hyporesponsiveness (i.e. tolerance) by transplanting a bone graft containing bone marrow cells at day 0 and administration of a costimulatory blockade (i.e. CTLA4-Ig and MR1 (anti-CD40L antibody)) at days 0, 2, 4, and 6. Under the experimental conditions described, the regimen induced graft tolerance at 30 weeks post transplantation.

Bingaman et al. did not teach use of T-cell depleted bone marrow as required by the claimed methods. Nor did Bingaman et al. teach, suggest or provide motivation for combining an alkylating agent with his regimen, nor the sequences of administration of the claimed invention, or doses of alkylating agents.

Applicants point out that a regimen similar to that disclosed by Bingaman et al. (e.g., with T cell depleted bone marrow instead of a bone graft) was described as a control in Examples 3 and 4 of the subject application. As shown in Examples 3 and 4 (Figures 4A and 5, respectively), providing only a combination of BM and a costimulatory blockade to a subject, similar to the regimen disclosed by Bingaman et al., is not as effective as the claimed methods of the invention, incorporating the administration of an alkylating agent. Accordingly, there was no expectation of success following the methods taught by

Bingamen et al. for the methods as claimed in the present invention. Moreover, the claimed methods provide unexpected advantages over the costimulation blockade taught by Bingaman et al.

Moreover, nothing in this disclosure provides "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" to support a finding of obviousness. KSR, 127 S.Ct. at 1731.

The combination of the Sykes '513 and Bingaman et al. reference does not render obvious the claimed methods.

Larsen et al., Curr. Opin. Immunol. 9:641-647

Larsen et al. teach the properties and distribution of CD40 and that the CD40 pathway plays a critical role in allograft rejection. The Larsen et al. reference is a review article summarizing the 1997 knowledge about CD40 and its pathway. Specifically, the reference teaches that inhibition of the CD40 pathway with an anti-CD40L mAb prolongs allograft survival and that simultaneous blockade of the CD40 and B7-CD28 costimulatory pathways inhibit allograft rejection.

Larsen does not teach or suggest what the primary reference fails to teach, namely, use of any amount of any alkylating agent, let alone busulfan, to facilitate mixed hematopoietic chimerism, subsequent to administration of T cell depleted bone marrow, or use of any alkylating agent, after a bone marrow transplantation. Accordingly, the combination of the Sykes and Larsen references, does not render obvious the claimed methods.

Schaub et al., J. Allergy and Clin. Immunol. 99:5206, abstract 843, 1997

Schaub et al. teach that simultaneous or sequential blockade of the CD28/B7 and CD40L/CD40 costimulatory pathway may synergistically affect EAE induction in mice. Specifically, mice were immunized with myelin basic protein and adjuvant to induce EAE on day 0, anti-CD40L antibody MR1 was administered on day 0 and 200 μg CTLA4Ig was administered on day 0 or 2. Administration of monotherapy (i.e. CTLA4Ig or MR1 alone) delayed disease onset and decreased disease severity, but, combination therapy with the sequential administration of MRI on day 0 and CTLA4Ig on day 2 resulted in synergistic inhibition of the autoimmune response in EAE over monotherapy.

Schaub et al. do not teach, suggest or provide motivation for adding an alkylating agent or T cell depleted bone marrow to a costimulatory blockade, nor the administration of the agents in a specific sequence, as taught by much the claimed invention. Nor do Schaub et al. teach the effective dosage of an alkylating agent for use in the claimed invention.

Accordingly, there was no expectation of success following the methods taught by Schaub et al. for the methods as claimed in the present invention. Moreover, the claimed methods provide unexpected advantages over the costimulation blockade taught by Schaub et al reference.

Moreover, nothing in this disclosure provides "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" to support a finding of obviousness. KSR, 127 S.Ct. at 1731.

Accordingly, the combination of the Sykes '513 and Schaub et al. reference does not render obvious the claimed methods.

ITEM 10: REJECTION UNDER 35 U.S.C. §103(a)

The Office rejects Claims 1, 9 and 33, under 35 U.S.C. §103(a), as allegedly unpatentable over Sykes et al. (U.S. Patent No. 6,514,513), in view of art known practice and modes of administration of alkylating agents such as busulfan/cyclophosphamide at various times to meet the needs of the patient, as acknowledged on pages 26-27 of the instant specification and as evidenced by Andersson et al. (U.S Patent Nos. 5,430,057 and 5,559,148) (1449, Exhibits 2 and 4), Slattery et al. (Therapeutic Drug Monitoring, 20:543-549, 1998), Hassan et al. (Blood 84:2144-2150, 1994), The Merck Manual of Diagnosis and Therapy, 17th Ed. (edited by Beers et al.), Shichi et al. (U.S. Patent No. 4,843,092), Strom et al. (Therapeutic Immunology edited by Austen et al.), Sykes et al. (Nature Medicine 3:783-787, 1997) and Wekerle et al. (J Exp Med, 187:2037-2044, 1998) and in further view of Reinherz et al. (U.S. Patent 4,443,427), Tomita et al. (J. Immunol. 164:34-41, 2000) (1449, Exhibit #274), Bingaman et al. (Transplantation 69:2491-2496, 2000) (1449, Exhibit #193), Larsen et al. (Curr. Opin. Immunol. 9:641-647) (1449, Exhibit #188) and Schaub et al. (J. Allergy and Clin. Immunol. 99:5206, abstract 843, 1997) (1449, Exhibit #264) and in view of Larsen et al. (US Patent No. 5,916,560) (1449, Exhibit #225).

Applicants respectfully disagree.

Sykes et al. (U.S. Patent No. 6,514,513), Andersson et al., Slattery et al., Hassan et al., The Merck Manual of Diagnosis and Therapy, 17th Ed., Shichi et al., Strom et al., Sykes et al. (Nature Medicine 3:783-787, 1997), Wekerle et al., Reinherz et al., Tomita et al., Bingaman et al., Larsen et al. (Curr. Opin. Immunol. 9:641-647) and Schaub et al. are distinguished above.

Larsen et al. (the '560 patent) teaches compositions and methods of inhibiting an immune response and tissue rejection by using a combination of two agents, wherein the first agent blocks the CTLA4/CD28/B7 pathway, and the second agent blocks the gp39/CD40 pathway. Specifically, the '560 patent show that costimulation blockade with MR1 and CTLA4 at days 0, 2, 4 (and in some experiments at day 6), prolonged graft survival.

The '560 patent fails to teach what the primary reference (Sykes '513) fails to teach, namely, any amount of busulfan that would facilitate mixed hematopoietic chimerism. Additionally, the '560 patent does not teach the administration of the agents in a specific sequence as in the claimed method. Further, the '560 patent does not teach or suggest the use of busulfan for inhibition or reduction of rejection of solid organ transplants.

Moreover, nothing in this disclosure provides "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" to support a finding of obviousness. KSR, 127 S.Ct. at 1731.

Therefore, the combination of Sykes '513 and the '560 patent does not render obvious the claimed methods.

ITEM 11: REJECTION UNDER 35 U.S.C. §103(a)

The Office also rejects claims 1, 5, 6, 9, 10, 12-23, 30, 34, 36-37, 44-52, 54-60, 62-63 and 64-74 under 35 U.S.C. §103(a) as allegedly unpatentable, over Sykes et al. (U.S. Patent No. 6,514,513), in view of art known practice and modes of administration of alkylating agents such as busulfan/cyclophosphamide at various times to meet the needs of the patient, as acknowledged on pages 26-27 of the instant specification and as evidenced by Andersson et al. (U.S Patent Nos. 5,430,057 and 5,559,148) (1449, Exhibits 2 and 4),

Slattery et al. (Therapeutic Drug Monitoring, 20:543-549, 1998), Hassan et al. (Blood 84:2144-2150, 1994), The Merck Manual of Diagnosis and Therapy, 17th Ed. (edited by Beers et al.), Shichi et al. (U.S. Patent No. 4,843,092), Strom et al. (Therapeutic Immunology edited by Austen et al.), Sykes et al. (Nature Medicine 3:783-787, 1997) and Wekerle et al. (J Exp Med, 187:2037-2044, 1998) and in further view of Reinherz et al. (U.S. Patent 4,443,427), Tomita et al. (J. Immunol. 164:34-41, 2000) (1449, Exhibit #274), Bingaman et al. (Transplantation 69:2491-2496, 2000) (1449, Exhibit #193), Larsen et al. (Curr. Opin. Immunol. 9:641-647) (1449, Exhibit #188) and Schaub et al. (J. Allergy and Clin. Immunol. 99:5206, abstract 843, 1997) (1449, Exhibit #264) and in view of Peach et al. (US 20020182211).

Applicants respectfully disagree.

Sykes et al. (U.S. Patent No. 6,514,513), Andersson et al., Slattery et al., Hassan et al., The Merck Manual of Diagnosis and Therapy, 17th Ed., Shichi et al., Strom et al., Sykes et al. (Nature Medicine 3:783-787, 1997), Wekerle et al., Reinherz et al., Tomita et al., Bingaman et al., Larsen et al. (Curr. Opin. Immunol. 9:641-647) and Schaub et al. are discussed above.

Peach et al. teach CTLA4 mutant molecules e.g., with mutations at position 29, and at position 104.

Peach et al. fail to teach what the primary reference fails to teach, namely, any effective amount of busulfan that facilitates mixed hematopoietic chimerism. Peach et al. also fail to describe the administration of agents in a specific sequence or dosage as in the present claims. Further, Peach et al. do not teach or suggest the use of any alkylating agent such as busulfan for inhibition or reduction of rejection of solid organ transplants.

Moreover, nothing in this disclosure provides "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" to support a finding of obviousness. KSR, 127 S.Ct. at 1731.

Therefore, the combination of the Sykes '513 and Peach et al. reference does not render obvious the claimed methods.

THE LEGAL STANDARDS FOR FINDING OBVIOUSNESS HAVE NOT BEEN MET BY THE OFFICE

The references in combination do not teach all of the claimed steps

The Office asserts that the claimed method is an obvious modification of the Sykes reference. However, as discussed *supra*, the prior art references in combination do not teach or suggest all of the claim limitations, in the sequence claimed, namely, steps a-d of claims 1, 9, 34, 55, 56, 62 or 63.

Moreover, Hassan et al. and Reinherz et al. teach away from the claimed method. Thus the combination of the prior art references does not render obvious the claimed method.

There was no suggestion to modify the prior art in order to obtain the claimed invention.

The Office's statement that it was within the skill in the art to make the modifications necessary to advance from the prior art to the claimed method is similar to an erroneous statement made in Ex parte Levengood.[1] In Levengood, the examiner stated that because the various aspects of the claimed process were individually known in the art (in the

[1] 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993).

instant case, this is not true), the modifications of a prior art process necessary to arrive at the claimed invention were "well within the ordinary skill of the art at the time the claimed invention was made."[2]

The Board of Patent Appeals and Interferences reversed the examiner's rejection because it was based on the wrong standard of obviousness: "At best, the examiner's comments regarding obviousness amount to an assertion that one of ordinary skill in the relevant art would have been able to arrive at appellant's invention because he had the necessary skills to carry out the requisite process steps. This is an inappropriate standard for obviousness. . . . That which is within the capabilities of one skilled in the art is not synonymous with obviousness."[3]

The Office's current reliance on what was within the skill in the art to support the obviousness of the modifications separating the prior art from the claimed invention is likewise an erroneous basis for finding the invention *prima facie* obvious over the cited art.

To establish a *prima facie* case of obviousness, the Office must present evidence that one skilled in the art would have been led to arrive at the claimed invention.[4] Mere unsupported arguments cannot take the place of evidence.[5]

In this regard, Sykes '513 merely suggests that other methods of creating hematopoietic space, e.g., administering hematopoietic space creating antibodies or drugs, e.g., cyclophosphamide or busulfan, to the recipient, can be used ('513 patent at column 5, lines 3-5). Without more, this statement cannot suggest the claimed invention. Merely

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[2] Id. at *1301*.
[3] Id. (citations omitted).
[4] Id.
[5] In re Wiseman, 596 F.2d 1019, 201 USPQ 658, 661 (CCPA 1979).

desiring an end result does not constitute a specific modification of the prior art. There is no description in Sykes '513 of the achievement of hematopoietic space using any of his suggested agents, nor guidance as to how to use a specific agent (e.g. dosage).

There is no evidence that any modification of the prior art would have led to a reasonable expectation of success in practicing the claimed invention.

It would not be enough to imply that, given the capabilities of those skilled in the art, it would have been obvious to try the claimed invention. In In re O'Farrell, the Federal Circuit gave examples of what would be obvious to try, but not obvious under 35 U.S.C. §103: "to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it."[6] O'Farrell clarified the additional requirement for a reasonable expectation of success.

Sykes provides only a suggestion to replace irradiation with busulfan as a preparative regimen for bone marrow transplants (BMT). This is very different from the claimed methods of inhibiting solid organ or/tissue/cellular transplants. None of the cited references, alone, or in combination, provides guidance for modifying the Sykes methods to achieve therapeutically effective methods as claimed. In fact, Hassan et al. teach that total body irradiation is superior to busulfan in terms of patient survival. Reinherz et al. teach away from the claimed invention by showing that even the use of a combination of two alkylating agents (i.e. busulfan and cyclophosphamide) with an anti-lymphocytic serum could not induce graft tolerance. Moreover, there was no reason to believe that busulfan dosages of the art as a preparative regimen for BMT would be extrapolatable for busulfan dosages for facilitating MHC in connection with solid organ transplants. Such speculative statements are not equivalent to a reasonable expectation of success, because

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[6] 853 F.2d 894, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

there was no direction or guidance on how to proceed to achieve the prophetic goal based on the references.

Additionally, Sykes '513 does not teach any specific sequence of administering the agents as in the presently claimed methods of the invention. The claimed method requires: administration of T cell depleted bone marrow to a subject; administration of an alkylating agent after the T cell depleted bone marrow to a subject; administration of additional T cell depleted bone marrow after the alkylating agent to a subject; and administration of a costimulatory blockade to the subject.

Further, Sykes fails to teach the use of busulfan together with other agents of the claimed methods for facilitating mixed hematopoietic chimerism, and the effective dosage of busulfan for such use.

As in Gangadharam, the Office in the present case is basing the rejection under Section 103 of the claimed methods on "a hopeful lead" allegedly provided by Sykes, a single prior art reference. Sykes' data using irradiation as a preparative regimen, cannot provide a reasonable expectation of success for the claimed method, for inhibiting rejection of a solid organ transplant in a subject. In fact, art cited by the Office teaches that radiation treatment is not equivalent to busulfan treatment (Hassan et al.).

The Office has not provided evidence that the prior art teaches or suggests *as a whole* the claimed methods. The claimed methods cannot be obvious over the cited references, because there was no suggestion regarding how to modify the prior art, in order to achieve the claimed methods. Moreover, even if it were obvious to try the combination of elements claimed, much less the specified sequence of administering the elements, without a reasonable expectation of success, a *prima facie* case of obviousness cannot be made. It is therefore, respectfully requested that the rejection under 35 U.S.C. §103, be

withdrawn, and that the claims be allowed.

THE CLAIMED INVENTION POSSESSES UNEXPECTED ADVANTAGES THAT THE CITED REFERENCES DO NOT TEACH

Applicants respectfully contend that the cited references do not render the claimed invention *prima facie* obvious. Furthermore, the alleged obviousness is rebutted by evidence of unexpected properties of the claimed invention (In re Davies and Hopkins, 475 F.2d 667, 177 U.S.P.Q. 381 (CCPA 1973)).

In addition to Applicants' previous showing, Applicants provide post filing confirmatory data showing that the methods of the invention possess superior properties. Specifically, Applicants provide the following:

1. Exhibit B: L. Kean et al.

> Here the authors show that nonmyeloablative preconditioning with busulfan (20mg/kg) coupled with costimulation blockade (CTLA4-Ig and anti-CD40L) can safely produce stable white blood cell (WBC) mixed chimerism and total replacement of the peripheral red cell compartment, resulting in a phenotypic cure of murine SCD. Furthermore, this cure is accomplished with fully major histocompatibility complex (MHC) mismatched donor marrow. Importantly, the hematologic cure that occurred with total replacement of the red cell compartment was accompanied by normalization of characteristic sickle organ pathology, indicating a total-body amelioration of disease.

2. Exhibit C: Z. Guo et al.

> The results of these studies demonstrate that the infusion of donor bone marrow together with busulfan and costimulation blockade (anti-CD40L mAb and CTLA4-Ig) induces hematopoietic chimerism and promotes the long-term survival of intestinal allografts transplanted into mice that have completed the treatment regimen. This long-term survival is associated with donor-specific hyporesponsiveness in vitro and deletion of donor-reactive T cells in vivo.

3. Exhibit D: N. Shirasugi et al.

> Treatment regimens consisting of costimulation blockade CB alone (CTLA4-Ig and anti-CD40L), CB and donor bone marrow cells (BMCs), and CB and donor splenocytes (DST) promote long-term allograft survival, but do not confer robust tolerance nor prevent chronic rejection in the face of a rechallenge with a donor skin graft. In contrast, a regimen consisting of CTLA4-Ig, anti-CD40L, donor BMCs, and a minimally myelosuppressive dose of busulfan produced stable donor-specific tolerance, and prevented both early and late cellular infiltration and chronic allograft vasculopathy, despite the rigorous rechallenge of a donor skin graft.

In view of the aforementioned discussion, Applicants respectfully request that the Patent Office reconsider and withdraw the rejection of the claims, under 35 U.S.C. §103.

ITEM 12: NO CLAIMS ALLOWED

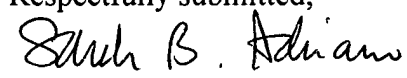
The Office has indicated that no claims have been allowed in the instant application. However, Applicants respectfully request that the Patent Office reconsider and withdraw the rejections of the claims for the reasons specified herein.

ITEM 13: INQUIRIES

If a telephone interview would be of assistance in advancing the prosecution of the subject application, Applicants undersigned attorney invites the Office to telephone her at the number provided below.

No fee, other than the $2,192.00 fee ($1,100.00 for the three-month extension of time and $1,092.00 for the excess claims fee), is deemed necessary in connection with the filing of this Amendment. If any additional fee is necessary, the Patent Office is authorized to charge the fee to Deposit Account No. 50-0306.

Respectfully submitted,



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